

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

9490-P28

Box No. I TITLE OF INVENTION

New process for the synthesis of perindopril and its pharmaceutically acceptable salts

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LES LABORATOIRES SERVIER
12, Place de la Défense
92415 COURBEVOIE Cedex
FRANCE

Telephone No.

01.55.72.60.00

Facsimile No.

01.55.72.72.13

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

FR

State (that is, country) of residence:

FR

This person is applicant
for the purposes of:

☐ all designated
States

☒ all designated States except
the United States of America

☐ the United States
of America only

☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DUBUFFET, Thierry
17, allée des Charmilles
76190 AUTRETOT
FRANCE

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

FR

State (that is, country) of residence:

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This person is applicant
for the purposes of:

☐ all designated
States

☐ all designated States except
the United States of America

☒ the United States
of America only

☐ the States indicated in
the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☐ agent

☒ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

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12, Place de la défense
92415 COURBEVOIE Cedex
FRANCE

Telephone No.

01.55.72.60.00

Facsimile No.

01.55.72.72.13

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LECOUVE, Jean-Pierre
93, rue du Docteur Vigné
76600 LE HAVRE
FRANCE

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:
FR

State *(that is, country)* of residence:
FR

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

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This person is:

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☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

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☐ inventor only *(If this check-box is marked, do not fill in below.)*

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☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

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This person is applicant for the purposes of:

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☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 10 December 2003 (10/12/03)	03293084.4		EP	
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| <input type="checkbox"/> Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| <input type="checkbox"/> Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| <input type="checkbox"/> Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| <input type="checkbox"/> Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| <input type="checkbox"/> Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

COMPLETED BY RO

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) on paper, the following number of sheets:

request (including declaration sheets) : 4

description (excluding sequence listing and/or tables related thereto) : [5] [4]

claims : 3

abstract : 1

drawings :

Sub-total number of sheets : [13] [12]

sequence listing :

tables related thereto :

(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)

Total number of sheets : [13] [12]

(b) ☐ only in electronic form (Section 801(a)(i))(i) ☐ sequence listing(ii) ☐ tables related thereto(c) ☐ also in electronic form (Section 801(a)(ii))(i) ☐ sequence listing(ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the

☐ sequence listing:☐ tables related thereto:

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

1. ☐ fee calculation sheet :2. ☒ original separate power of attorney : 13. ☐ original general power of attorney :4. ☐ copy of general power of attorney; reference number, if any:5. ☐ statement explaining lack of signature :6. ☒ priority document(s) identified in Box No. VI as item(s):7. ☐ translation of international application into (language):8. ☐ separate indications concerning deposited microorganism or other biological material :9. ☐ sequence listing in electronic form (indicate type and number of carriers)(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers)(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :11. ☐ other (specify):

Number of items

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

French

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

(signature)

Odile OSTERMANN, authorised signatory LES LABORATOIRES SERVIER

For receiving Office use only

1. Date of actual receipt of the purported international application:

(09-12-2004)
9 DEC. 2004

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

2. Drawings:

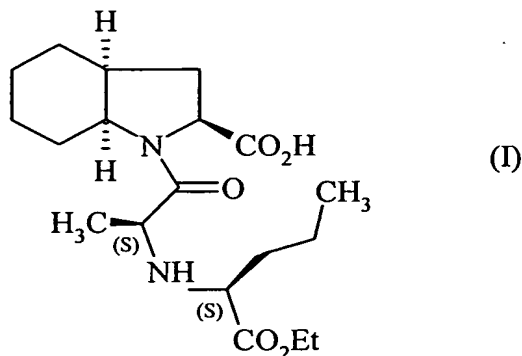
☐ received:☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

The present invention relates to a process for the synthesis of perindopril of formula (I) :



and pharmaceutically acceptable salts thereof.

- 5 Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

- 15 Perindopril, its preparation and its use in therapeutics have been described in European patent specification EP 0 049 658.

In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and, especially, with excellent purity.

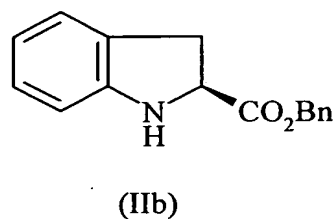
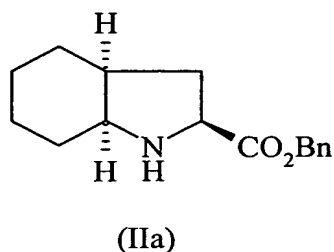
- 20 Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the coupling of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester with N-[(S)-1-

carboxybutyl]-(*S*)-alanine ethyl ester in the presence of dicyclohexylcarbodiimide, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

That process has disadvantages related to use of the dicyclohexylcarbodiimide.

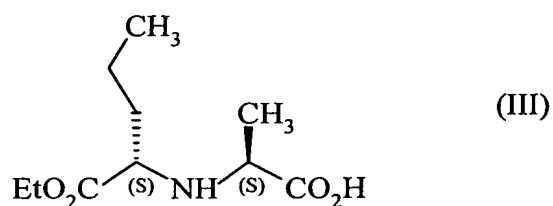
- 5 The Applicant has developed a process for the synthesis of perindopril that uses other coupling agents.

More specifically, the present invention relates to a process for the synthesis of perindopril, which process is characterised in that the benzyl ester of formula (IIa) or (IIb) :



- 10 or an addition salt of the ester of formula (IIa) or (IIb) with a mineral acid or organic acid is reacted

with the compound of formula (III) :



- 15 in the presence of a coupling agent selected from the following reagents and pairs of reagents :

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxybenzotriazole,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxy-7-azabenzotriazole,

- 20 (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxysuccinimide,

- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxyphthalimide,
dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,
5 dicyclohexylcarbodiimide / N-hydroxysuccinimide,
dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
dicyclohexylcarbodiimide / N-hydroxyphthalimide,
O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
10 O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate,
15 chloro-tripyrrolidinophosphonium hexafluorophosphate,
chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate,
chloro-1,1,3,3-bis(pentamethylene)formamidinium hexafluorophosphate,
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline,
O-[(ethoxycarbonyl)-cyanomethyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate,
20 O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
tetrafluoroborate,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
tetrafluoroborate / 1-hydroxybenzotriazole,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
25 tetrafluoroborate / N-methylmorpholine,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
tetrafluoroborate / collidine,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate /
30 1-hydroxybenzotriazole,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluoro-phosphate / 1-hydroxy-benzotriazole,

O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate,

5 O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate / 1-hydroxy-benzotriazole,

O-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate, propanephosphonic anhydride,

N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide,

10 and N-hydroxy-1,2-dihydro-2-oxo-pyridine,

optionally in the presence of a base,

to yield, after catalytic hydrogenation in the presence of palladium, perindopril of formula (I), which is converted, if desired, into a pharmaceutically acceptable salt such as the tert-butylamine salt.

15 When the compound of formula (IIa) is used as starting material, the catalytic hydrogenation is preferably carried out under a hydrogen pressure of less than 10 bars.

When the compound of formula (IIb) is used as starting material, the catalytic hydrogenation is preferably carried out under a hydrogen pressure of from 10 to 35 bars.

The example hereinbelow illustrates the invention.

20 **Example 1 :** *Benzyl (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(ethoxycarbonyl)-butylamino]-propionyl}-octahydro-1H-indole-2-carboxylate :*

200 g of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester para-toluene-sulphonate, 65 ml of triethylamine and 1 litre of ethyl acetate are introduced into a stirred reactor, followed, after stirring for 10 minutes at ambient temperature, by 100 g of N-[(S)-ethoxycarbonyl-1-butyl]-(S)-alanine and 175 g of O-(benzotriazol-1-yl)-1,1,3,3-bis(tetra-

25

methylene)uronium hexafluorophosphate. The heterogeneous mixture is then heated at 30°C for 3 hours whilst stirring well and is then cooled to 0°C and filtered.

The filtrate is then washed and subsequently evaporated to dryness to yield the expected product.

5 **Example 2** : *(2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)-butylamino]-propionyl]-octahydro-1H-indole-2-carboxylic acid* :

The residue obtained in the previous step (200 g) is dissolved in 200 ml of methylcyclohexane and transferred to a hydrogenator; 26 g of 5 % palladium-on-carbon suspended in 80 ml of methylcyclohexane are then added, followed by 640 ml of water.

10 The mixture is then hydrogenated under a pressure of 0.5 bar at a temperature of from 15 to 30°C, until the theoretical amount of hydrogen has been absorbed.

After filtering off the catalyst, the aqueous phase of the filtrate is washed with methylcyclohexane and then lyophilised to yield the expected product in a yield of 94 %.

15 **Example 3** : *(2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(Ethoxycarbonyl)-butylamino]-propionyl]-octahydro-1H-indole-2-carboxylic acid tert-butylamine salt* :

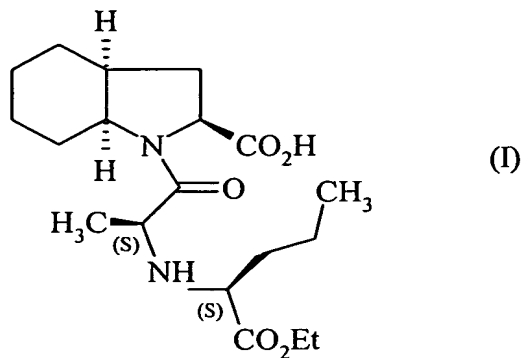
The lyophilisate obtained in the previous step (200 g) is dissolved in 2.8 litres of ethyl acetate, and then 44 g of tert-butylamine and 400 ml of ethyl acetate are added.

The suspension obtained is then refluxed until dissolution is complete; then the solution obtained is filtered whilst hot and cooled to a temperature of 15-20°C, with stirring.

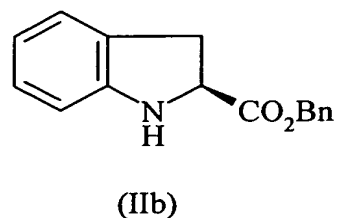
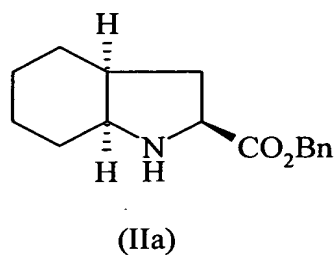
20 The precipitate obtained is then filtered off, made into a paste again using ethyl acetate, dried and then ground to yield the expected product in a yield of 95 %.

CLAIMS

1. Process for the industrial synthesis of perindopril of formula (I)

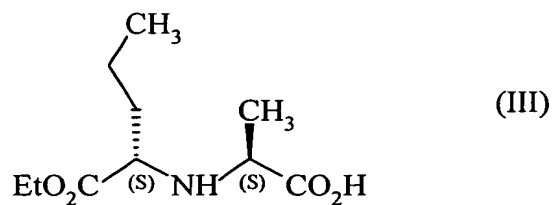


and pharmaceutically acceptable salts thereof, characterised in that the benzyl ester of
5 formula (IIa) or (IIb) :



or an addition salt of the ester of formula (IIa) or (IIb) with a mineral acid or organic acid
is reacted

with the compound of formula (III) :



10

in the presence of a coupling agent selected from the following reagents and pairs of
reagents :

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(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxybenzotriazole,

- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxy-7-azabenzotriazole,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxysuccinimide,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 3-hydroxy-3,4-dihydro-
5 4-oxo-1,2,3-benzotriazine,
- (1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxyphthalimide,
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dicyclohexylcarbodiimide / N-hydroxysuccinimide,
dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
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O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
15 benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate,
chloro-tripyrrolidinophosphonium hexafluorophosphate,
chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate,
20 chloro-1,1,3,3-bis(pentamethylene)formamidinium hexafluorophosphate,
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O-[(ethoxycarbonyl)-cyanomethyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
tetrafluoroborate,
25 O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
tetrafluoroborate / 1-hydroxybenzotriazole,
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
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O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium
30 tetrafluoroborate / collidine,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate /
1-hydroxybenzotriazole,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluoro-
5 phosphate / 1-hydroxy-benzotriazole,
O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate,
O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate / 1-hydroxy-
benzotriazole,
10 O-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate,
propanephosphonic anhydride,
N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide,
and N-hydroxy-1,2-dihydro-2-oxo-pyridine,

optionally in the presence of a base,

15 to yield, after catalytic hydrogenation in the presence of palladium, perindopril of
formula (I), which is converted, if desired, into a pharmaceutically acceptable salt.

2. Process according to claim 1 for the synthesis of perindopril in the form of its tert-
butylamine salt.

3. Process according to claim 1, characterised in that the compound of formula (IIa) is
20 used as starting material.

4. Process according to claim 1, characterised in that the compound of formula (IIb) is
used as starting material.

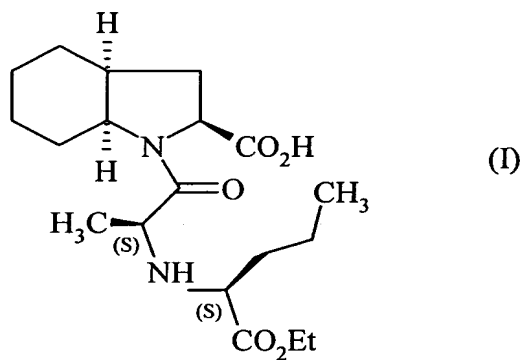
5. Process according to claim 3, characterised in that the hydrogenation reaction is carried
out under a hydrogen pressure of less than 10 bars.

25 6. Process according to claim 4, characterised in that the hydrogenation reaction is carried
out under a hydrogen pressure of from 10 to 35 bars.

ABSTRACT

**NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL
AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF**

Process for the industrial synthesis of perindopril of formula (I) :



5

and pharmaceutically acceptable salts thereof.